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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,326	08/28/2003	Keith A. Hruska	STK-P01-599	6882

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,326	HRUSKA ET AL.	
	Examiner	Art Unit	
	Christina Borgeest	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56,69-71,76 and 78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56,69-71,76 and 78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/15/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11 July 2008 has been entered.

Rejections Withdrawn

All rejections of record over claims 72-75 are withdrawn in response to Applicants' cancellation of those claims.

Rejections Maintained

Claim Rejections - 35 USC § 103

Note that Applicants' Arguments will be addressed at the end of the two rejections under 35 U.S.C. 103, since they are directed at both.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 56 and 70-71, 76 and 78 under 35 U.S.C. 103(a) as being unpatentable over Sampath et al. (U.S. Patent No: 6,498,142, filed 6 May 1996—of record) and London et al. (Journal of hypertension. 1996; 14: 1139-46—of record) as set forth in previous Office actions (mailed 21 September 2006 and 11 June 2007) is maintained for reasons of record and the following. The amended claims are drawn to a pharmaceutical composition comprising a therapeutically effective amount of an ACE inhibitor and an OP/BMP morphogen, wherein the combination of said ACE inhibitor and BMP mrophogen is capable of inducing a synergistic effect on reducing proteinuria

levels in a diabetic nephropathy model (as recited in claim 56) formulated with pharmaceutically acceptable salt, carrier, excipient or diluent (claim 76) wherein the morphogen is the polypeptide of SEQ ID NO: 3 (claim 70), or wherein the morphogen is a first polypeptide including at least a C-terminal cysteine domain of a protein selected from: a pro form, a mature form, or a soluble form of a second polypeptide, wherein said second polypeptide is: OP-1, OP-2, OP-3, BMP2, BMP3, BMP4, BMP5, BMP6, or BMP9 (claim 71), in association with instructions for administering the composition to a mammal for treatment or prevention of chronic renal failure (claim 78—note that written instructions are not statutory subject matter in a patent, thus are given no patentable weight).

When deciding whether claims are obvious, the first factor that must be considered is to determine the scope and contents of the prior art. Sampath et al. teach methods and pharmaceutical preparations for use in the treatment of mammalian subjects at risk of chronic renal failure comprising administration of OP-1 formulated with appropriate excipients (as well as other BMPs and/or OPs—see the claims; column 24, lines 30-67 and SEQ ID NO: 16 which has 100% sequence similarity with SEQ ID NO: 3 of the instant application and encompasses the C-terminal seven cysteine domain recited in claim 71. Sampath et al. further teach the exact same BMP morphogens at columns 11 lines 62-67 through 12, lines 1-17 as those recited in amended claim 56. Sampath et al. discuss at columns 21-24 that subjects indicated for treatment are those at risk of renal failure, and teaches measuring glomerular filtration rate or GFR as a method of estimating renal function. Finally, Sampath et al. teach at

column 29, lines 3-36 that GFR showed OP-1 treated animals stabilized compared to controls and treated animals fared significantly better than controls by week 5 and that histological evaluation of renal tissue confirmed that OP-1 treatment preserved or maintained glomeruli, proximal and distal tubule structures and showed reduced degeneration. In summary, Sampath et al. provide evidence of successful attenuation of renal failure in an art-accepted model for renal failure.

The second factor that must be considered is to ascertain the difference between the prior art and the claims at issue. Sampath et al. do not teach a pharmaceutical composition that also comprises an ACE inhibitor, nor do they teach that the combination synergistically lowers proteinuria levels in a diabetic nephropathy model. London et al. teach the administration of ACE inhibitors (specifically, they administer quinapril) for the treatment of hypertensive individuals with end-stage renal disease (see p. 1140, left column, 3rd paragraph) with the effect that ACE inhibition resulted in more efficient ventricular-vascular coupling and decreased left ventricular load. A packaged pharmaceutical is encompassed by the claims because each of the teachings suggest the administration of measured amounts of the compositions, thus encompass "packaged". In summary, London et al. teach that ACE inhibition improves blood pressure in patients with renal disease, a condition which is often complicated with hypertension (see abstract of London et al.).

The new limitation that the combination of ACE inhibitor and BMP morphogen synergistically lowers proteinuria levels in a diabetic nephropathy model segues into a discussion of the third factor that must be considered, which is to resolve the level of

ordinary skill in the art. Given the teachings of both Sampath et al. and London et al., it is clear that the person of ordinary skill in the art, or POSITA, would recognize that both BMP morphogens and ACE inhibitors are indicated for those suffering from renal disease. Furthermore, the POSITA would recognize that renal disease is known to be complicated with hypertension. The POSITA would be motivated to administer a combination of BMP morphogens and ACE inhibitors to patients with renal disease because Sampath et al. teach BMP morphogens attenuate renal failure and London et al. teach that ACE inhibition improves blood pressure in patients with renal disease, thus the claims would have been obvious because the POSITA has good reason to pursue known options within his or her technical grasp. If this leads to anticipated success, it is likely to be the product not of innovation but of ordinary skill and common sense. Although neither Sampath et al. nor London et al. teach or suggest that this combination would lower proteinuria, the claims are drawn to a product and the ability of this product (BMP morphogen + ACE inhibitor) to lower protein in the urine is intrinsic to the functioning of this combination. As stated above, the discussed prior art disclose that both BMP morphogens and ACE inhibitors are indicated for the treatment of renal disease, and the POSITA would be motivated to administer them in combination. Furthermore, the specification does not define "synergistic", nor are there any numerical values recited in the claims to put a threshold on the "synergistic effect", thus a reasonable interpretation of this term is that any effect that is more than additive can be considered synergistic. See for instance, Bell (FEMS Microbiology Letters. 2005; 253: 171-184—of record), who wrote:

> "Therein lies another problem with many studies on antimalarial drug interactions, which is that synergism (or antagonism) can be taken to mean almost anything the investigator wants it to mean. For example, synergism between two agents is often taken as evidence that the relevant targets of the two agents form components of a common pathway. This may be true, but it has been argued that sequential inhibition of linear reactions in metabolic pathways by two or more inhibitors in the steady state alone cannot be synergistic (see discussion of antifolates below), so it is not necessarily so. Another liberty taken is to conclude from data showing antagonism between drugs A and B that the two drugs have a common target. One could also argue (as in example (i) above) that the same conclusion could be drawn from a synergistic interaction, or (returning to the case where A = B) from no interaction. Therefore, in the discussion of specific antimalarial drugs below, mechanistic inferences made from drug interaction data will be treated with caution unless there is a logical explanation and at least some supporting evidence for the effect.".

The rejection of claim 69 under 35 U.S.C. 103(a) as being unpatentable over Sampath et al. (U.S. Patent No: 6,498,142) and London et al. (Journal of hypertension. 1996; 14: 1139-46) as applied to claims 56 and 70-76 and 78 in the immediately preceding paragraph and Salvetti (Drugs. 1990; 40: 800-28—of record) as set forth in previous Office actions (mailed 21 September 2006 and 11 June 2007) is maintained for reasons of record and the following. Claim 69 limits the ACE inhibitor to enalpril.

The discussion above regarding how Sampath et al. and London et al. meet the limitations of claims 56, 70, 71, 76 and 78 is applicable here and hereby incorporated. The prior art differs from the claims in that neither Sampath et al. nor London et al. teach that the ACE inhibitor is enalapril. Salvetti et al. review and compare the ACE inhibitors, including enalapril, thus this article suggests the similarity of action between ACE inhibitors on the market. Note especially, p. 802, whole page, which contains a

discussion on the biochemistry and pharmacokinetics of ACE inhibitors. Note also, p. 802, right column, 3rd paragraph, where it is said that enalapril is more potent and has a longer duration of action. Given the teachings of Sampath et al. and London et al., which suggest that BMP morphogens and ACE inhibitors, respectively, are useful for treating renal disease, it would have been obvious to the POSITA at the time the invention was made to modify the teachings of Sampath et al. and London et al. by formulating a pharmaceutical containing the ACE inhibitor, enalapril, as taught in Salvetti, because Salvetti states that enalapril is more potent and has a longer duration of action (p. 802, right column, 3rd paragraph) and additionally, Salvetti suggests the similarity of the many commercially available ACE inhibitors, thus the knowledge of their pharmacokinetics and efficacy for reducing hypertension with many species of ACE inhibitors were well known in the art at the time of filing. The person of ordinary skill in the art would have been motivated to make the change because renal disease because of the greater potency and duration of enalapril, and for this reason as well, the person of ordinary skill in the art could have reasonably expected success.

Applicants argue at p. 8, 1st paragraph that neither Sampath et al. nor London et al. teach or suggest a greater than additive effect for the BMP morphogen and ACE inhibitor combination.

This argument has been fully considered but is not found persuasive. As outlined at p. 3 of the Final Rejection (mailed 11 June 2007), the showing should demonstrate that synergism is unexpected. See *In re Huellmantel*, 324 F.2d 998, 139 USPQ 496 (CCPA 1963); *In re Meinhardt*, 392 F.2d 273, 157 USPQ 270 (CCPA 1968).

A greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent. Applicants arguments do not outline why the synergy between OP-1 and enalapril would be unexpected, especially given that the prior art teaches both of these agents are useful in the treatment of renal disease.

Applicants argue at p. 9, 1st paragraph that based on Hruska et al. (2000—of record) one of skill in the art would not have been motivated to use enalapril and OP-1 together or expect that the combination would have a synergistic effect because OP-1 performed better or equal to enalapril in a number of assays.

This argument has been fully considered but is not found persuasive. The teaching of Hruska et al. does not illuminate why synergy would be unexpected because the assays do not address proteinuria. In fact, according to p. F130, right column, 2nd paragraph, the authors state that they used the unilateral uretreral obstruction or UUO model of renal injury because "hypertension, ***proteinuria*** and lipid dysregulation do ***not*** contribute to progressive nephron destruction." (Emphasis added). In other words, the model used in Hruska et al. was one in which the animals do not suffer from "the complex milieu of renal diseases" that are often found in patients with renal disease. The POSITA would not necessarily look at this model as representative of patients with renal disease, and therefore would not conclude that a combination of BMP morphogen and ACE inhibitor should not be administered based on a reading of Hruska et al. Sampath et al. teach that the BMP morphogen, OP-1 attenuates renal injury in an art accepted model of renal failure and London et al. teach that ACE

inhibition treats hypertension, a condition that is part of the "complex milieu of renal diseases," in patients with end stage renal disease. In fact, there is support in the prior art for the ability of ACE inhibitors to treat proteinuria in hypertensive patients. For instance, see Eberhard Ritz, (American Journal of Hypertension, 1995; 8: 53S-8S), which teaches that ACE inhibitors lower proteinuria and that because "combination therapy is required in most patients with advanced renal failure, recent experimental studies on development and glomerular sclerosis and clinical studies showing at least additive effects on reduction of proteinuria independent of blood pressure argue for combining ACE inhibitors and calcium antagonists." (See abstract, p. 54S, left column, 1st paragraph; right column, 1st paragraph). Also see de Zeeuw et al. (Canadian Journal of Cardiology, 1995; 11(Suppl. F): 41F-4F), who teach "ACE inhibitors appear to be the drugs of choice since they not only lower blood pressure but also reduce some important risk factors that may cause progressive loss or renal function, such as...proteinuria. Indeed, several clinical studies now show that ACE inhibitors offer renal protection beyond the lowering of systemic blood pressure." (See abstract, p. 43F, left column, 1st 3 paragraphs). In other words, Ritz and de Zeeuw et al. provide further evidence that it was known in the art that ACE inhibition was not only useful for treatment of hypertension but also attenuating renal injury (e.g. proteinuria) in individuals with diabetic nephropathy at risk for renal failure. Thus the argument that the POSITA would not be motivated to use enalapril and OP-1 together based on Hruska et al. is not convincing.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Note that Applicant's arguments regarding obviousness type double patenting rejections over U.S. Patent No. 6,677,432 and U.S. Patent No. 6,846,906 will be addressed after the rejections.

The rejection of claims 56, 71, 76 and 78 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,677,432 in view of in view of London et al. (of record) and Vukicevic et al. (of record) is maintained for reasons of record and the following.

The rejection of claims 56 and 69 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6,677,432 in view of in view of London et al. (of record) as applied to claims 56, 71-76 and 78 in the immediately preceding paragraphs and further in view of Vukicevic et al. and Salvetti (both of record) is maintained for reasons of record and the following.

The rejection of claims 56, 71, 76 and 78 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,846,906 in view of in view of London et al. (of record) and Vukicevic et al. (of record) is maintained for reasons of record and the following.

The rejection of claims 56 and 69 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,846,906 in view of in view of London et al. (of record) as applied to claims 56, 71-76 and 78 in the immediately preceding paragraphs and further in view of Vukicevic et al. and Salvetti (of record) is maintained for reasons of record and the following.

With regard to these rejections, Applicants argue that:

1) Claim 56 has bee amended to recite an ACE inhibitor together with specific BMPs, wherein the combination is capable of inducing a synergistic effect on reducing proteinuria levels in a diabetic nephropathy model and not OP-1 mutants or TGF-β chimeras (see p. 11, 2nd and 4th paragraphs; p. 13, last paragraph).

2) Claims 1-13 of the '432 patent are directed to OP-1 mutants and the claims of the '906 patent are directed to TGF-β chimeras, respectively (see p. 11, 3rd paragraph; p. 13, last paragraph).

3) The synergistic effect on reducing proteinuria levels using the combination of ACE inhibitor with specific BMPs is not taught or suggested by patented claims and the POSITA would have no reason to expect would have a synergistic effect t on reducing proteinuria levels (see p. 12, 2nd paragraph; p. 14, last paragraph; p. 18, last 2 paragraphs; p. 20, 1st paragraph).

These arguments have been fully considered but are not found persuasive.

Regarding arguments 1 and 2, Vukicevic teaches the specific morphogen, OP-1, for example. Regarding argument 3, as discussed above, Applicants have not made a convincing argument as to why the synergistic effect would be unexpected. The prior art suggest otherwise. For instance, see Eberhard Ritz, (American Journal of Hypertension, 1995; 8: 53S-8S), which teaches that because "combination therapy is required in most patients with advanced renal failure, recent experimental studies on development and glomerular sclerosis and clinical studies showing at least additive effects on reduction of proteinuria independent of blood pressure argue for combining ACE inhibitors and calcium antagonists." (See abstract, p. 54S, left column, 1st paragraph; right column, 1st paragraph). Also see de Zeeuw et al. (Canadian Journal of Cardiology, 1995; 11(Suppl. F): 41F-4F), who teach "ACE inhibitors appear to be the drugs of choice since they not only lower blood pressure but also reduce some important risk factors that may cause progressive loss or renal function, such as…proteinuria. Indeed, several clinical studies now show that ACE inhibitors offer renal protection beyond the lowering of systemic blood pressure." (See abstract, p. 43F, left column, 1st 3 paragraphs). In other words, Ritz and de Zeeuw et al. provide further evidence that it was known in the art that ACE inhibition was not only useful for treatment of hypertension but also attenuating renal injury (e.g. proteinuria) in

individuals with diabetic nephropathy and at risk for renal failure. Given the teachings that ACE inhibition protected against renal injury, the POSITA could well expect synergism from the combination of BMP morphogens and ACE inhibitors.

The provisional rejection of claims 56, 71, 76 and 78 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 16-18 of copending Application No. 10/816,768 in view of in view of London et al. and Vukicevic et al (both of record) is maintained for reasons of record and the following.

Applicants argue at p. 16, 2nd paragraph that the claims of the '768 application do not recite treatment of renal disease.

This argument has been considered but is not found persuasive. The instant claims are drawn to products, not methods, so intended use is not relevant.

Applicants argue at p. 16, 2nd and 3rd paragraphs that claims 10 and 16-18 of the '768 application do not recite OP-1 and/or morphogens as suggested by the Examiner.

This argument has been considered but is not found persuasive. In fact, claims 10 and 16-18 of the '768 application recite the same BMP morphogens as newly amended claim 56, for instance, note claim 18.

Applicants argue at p. 17, 1st paragraph that the combination of claims 10 and 16-18 of the '768 application and London et al. and Vukicevic et al. do teach a combination of ACE inhibitor with a TGF mutant.

This argument has been fully considered but is not found persuasive. In fact, claim 18 of the '768 application, for example, recites the same BMP morphogens as

newly amended claim 56, so claims 10, 16-18 of the '768 application with London et al. and Vukicevic teach the same combination as recited in the instant claims.

Applicants argue at p. 17, 2nd paragraph that the combination of claims 10 and 16-18 of the '768 application and London et al. and Vukicevic et al. do not teach or suggest the synergistic effect recited in the instant claims.

As discussed above, Applicants have not made a convincing argument as to why the synergistic effect would be unexpected. The prior art suggest otherwise. For instance, see Eberhard Ritz, (American Journal of Hypertension, 1995; 8: 53S-8S), which teaches that because "combination therapy is required in most patients with advanced renal failure, recent experimental studies on development and glomerular sclerosis and clinical studies showing at least additive effects on reduction of proteinuria independent of blood pressure argue for combining ACE inhibitors and calcium antagonists." (See abstract, p. 54S, left column, 1st paragraph; right column, 1st paragraph). Also see de Zeeuw et al. (Canadian Journal of Cardiology, 1995; 11(Suppl. F): 41F-4F), who teach "ACE inhibitors appear to be the drugs of choice since they not only lower blood pressure but also reduce some important risk factors that may cause progressive loss or renal function, such as...proteinuria. Indeed, several clinical studies now show that ACE inhibitors offer renal protection beyond the lowering of systemic blood pressure." (See abstract, p. 43F, left column, 1st 3 paragraphs). In other words, Ritz and de Zeeuw et al. provide further evidence that it was known in the art that ACE inhibition was not only useful for treatment of hypertension but also attenuating renal injury (e.g. proteinuria) in individuals with diabetic nephropathy and at risk for renal failure. Given the teachings that ACE inhibition protected against renal injury, the

POSITA could well expect synergism from the combination of BMP morphogens and ACE inhibitors.

The rejection of claims 56 and 69 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10 and 16-18 of copending Application No. 10/816,768 in view of in view of London et al. (of record) as applied to claims 56, 71-76 and 78 in the immediately preceding paragraphs and further in view of Vukicevic et al. and Salvetti (both of record) is maintained for reasons of record.

Applicants have presented the same arguments at pages 20-21 with regard to claim 69 as were presented at pages 16-17, and the Examiner's remarks in the immediately preceding paragraphs regarding claims 56, 71, 76 and 78 are hereby incorporated.

Conclusion

No claim is allowed.

Application 10/650,326 is a continued examination. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Borgeest whose telephone number is (571)272-4482. The examiner can normally be reached on 8:00am - 2:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Christina Borgeest, Ph.D.

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646